IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

CHIRON CORPORATION,

Plaintiff,

v.

SOURCECF INC., SOURCECF CLINICAL RESEARCH & DEVELOPMENT, L.L.C., MAXOR NATIONAL PHARMACY SERVICES CORPORATION d/b/a IV SOLUTIONS, FOUNDATION CARE L.L.C., and PHARMACEUTICAL SPECIALTIES, INC.,

Defendants.
_____/

No. C 05-01938 WHA

FINDINGS OF FACT AND CONCLUSIONS OF LAW AFTER BENCH TRIAL

INTRODUCTION

The issue presented is the extent to which cystic fibrosis victims, their parents and their doctors are barred by a medical-method patent asserted by Chiron Corporation from using inhaled tobramycin to treat lung infections. Cystic fibrosis victims, their parents and their physicians have long used inhaled antibiotics to treat lung infections. Tobramycin and nebulizers were known well before the invention in question. Neither was invented by Chiron. A drug-device combination using tobramycin with a particular nebulizer came on the market in 1997. Chiron later acquired it and has successfully marketed the combination as TOBI. It is prior art for purposes of Chiron's later patent asserted herein.

More efficient and more portable nebulizers have been invented by others. Being more efficient, the new nebulizers can cut the treatment duration at least in half. The shorter treatment duration encourages children to comply with their treatment regimens. The new nebulizers are also small and portable, unlike the heavy TOBI machine. It seems undisputed between the parties that the new generation of nebulizers represents an improvement.

Despite this development, Chiron has not come out with a new drug-device combination using a new nebulizer. Instead, it has continued to promote TOBI, which still enjoys a dominant market position. Chiron has, however, successfully sought and obtained a recent medical-method patent to prevent CF victims, their parents and their physicians from using the new generation of nebulizers with tobramycin, or at least from using those treatment methods within the limits of the claims.

Chiron does not claim to have invented tobramycin or a nebulizer of any type. Rather, Chiron claims to have discovered safe and efficacious concentrations of tobramycin for use in the new nebulizers. Chiron based its patent application on three clinical studies. The clinical studies vetted reduced volumes of Chiron's standard TOBI solution with more efficient nebulizers. These studies were eventually published as the disclosure in the patent in suit. Significantly, all of the studies involved tobramycin concentrations of 60 mg/ml or 120 mg/ml. All of the claims called out concentrations of "about 60 mg/ml" or higher. No study in the patent vetted weaker concentrations. No claim called out weaker concentrations.

Through the patent in suit, Chiron asserts that CF victims, their parents and their physicians are barred from using any treatment method administering tobramycin via the new and efficient nebulizers when the total dose to be nebulized is four milliliters or less *and* the concentration of tobramycin to solution is within the range of "about 60 mg/ml to about 200 mg/ml." The accused methods of treatment at issue herein, however, all involve concentrations *below* 60 mg/ml. In one, CF victims, their parents and doctors use a concentration of 50 mg/ml. In the other, the concentration is 40 mg/ml. The issue for decision is whether Chiron's patent covers and therefore bars use of these methods involving weaker concentrations.

The issue is important to Chiron because its sole entry in the relevant market is TOBI. Although, as stated, Chiron does not sell products for use with the patented method, the emergence of the new class of better nebulizers poses a threat to TOBI's dominant market share.

After a bench trial, this order holds that Chiron's patent does not cover the weaker concentrations at issue in this suit. It is true that the lower concentrations seem safe and efficacious. But the patent is limited by the concentrations actually claimed. The patent does not go so far as to claim *all* safe and effective doses regardless of concentration. The injunction sought by Chiron must be denied.

FINDINGS OF FACT AND PROCEDURAL HISTORY[1]

The patent in suit is United States Patent No. 6,890,907 ("the '907 patent"), owned by Chiron Corporation. The '907 patent purportedly discloses a method of treating lung infections, namely using certain concentrations of liquid tobramycin with high-efficiency nebulizers, for patients suffering from cystic fibrosis.

Cystic fibrosis strikes children. The symptoms manifest in early childhood. The average life expectancy of CF patients is thirty-five years. Approximately 30,000 children and adults in the United States currently suffer from CF.

CF causes mucus in the airways to become thick, dry, and sticky. The mucus builds up rather than continually refreshing itself as would be normal. The buildup is unhealthy, especially in the lungs. The lungs become breeding grounds for harmful bacteria. The most significant of these pathogens is *Pseudomonas aeruginosa*.

Well before the alleged invention, physicians administered and pharmacists dispensed antibiotics to CF patients to treat pulmonary infections including *Pseudomonas aeruginosa*.

[1] Although voluminous proposed findings were submitted and considered, this order finds its own way and makes its own findings rather than picking and choosing between the competing versions. That a proposed finding has not been expressly incorporated does not necessarily mean it has been rejected; rather it means that this order has found it unnecessary to adopt or reject it per se. To the extent, however, that any proposed finding was expressly admitted by the responding party in the most recent round of proposals and responses, this order hereby adopts the proposal (to the extent expressly admitted). It is unnecessary for this order to cite the record and it will not do so except to particulars that may assist the court of appeals.

The most successful of such antibiotics was (and remains) tobramcyin. Tobramycin, however, is poorly absorbed across mucosal surfaces.

In the early 1990's, therefore, physicians began administering tobramycin to CF patients via inhalation therapy. The total doses of tobramycin used at that time ranged from 80 mg to 400 mg. The tobramycin was dissolved in a solution. The doctor would prescribe a concentration, for example, "100 mg/ml" or state "200 mg in 2 ml of saline solution" (which would translate to a concentration of 100 mg/ml). Pharmacists would dispense concentrations pursuant to physicians' orders. A brand-name version of tobramcyin for inhalation in the early 1990's was NEBCIN, which came in either a 40 mg/ml concentration in 2 ml volume or in a powder form to allow pharmacists to dispense the medication pursuant to a physician's specifications. NEBCIN was part of the prior art. It was not Chiron's product.

The primary inhalation device available for tobramycin in the early 1990's was the jet nebulizer. A nebulizer is an apparatus that converts a liquid (such as a medication) into aerosol droplets. A jet nebulizer uses gas flow through an aperture to pick up and atomize a solution. Pari Respirator Equipment, Inc. manufactured one such jet nebulizer known as the Pari LC Plus.

Prior to any application for the '907 patent, an earlier patent issued on April 16, 1996, relating to an antibiotic solution for aerosolization for CF patients. This was United States Patent No. 5,508,269 ("the '269 patent"). That patent was obtained by PathoGenesis, later acquired by plaintiff Chiron. The '269 is prior art for our purposes. The '269 described an antibiotic solution for inhalation, limited by amount of antibiotic, total volume, nebulization method and particle size.

On December 22, 1997, the Food and Drug Administration approved TOBI as a drug-device combination. TOBI was essentially the drug-device combination described in the '269 patent. TOBI is a particular concentration of tobramcyin solution for inhalation in the Pari LC Plus. The marketed version of TOBI contained 300 mg/ml of tobramcyin in 5 ml of quarter saline solution, *i.e.*, a concentration of 60 mg/ml. The FDA's approval allowed marketing of TOBI, without deviation. In other words, PathoGenesis (and later Chiron) could not advertise or make representations about the safety and efficacy of any concentration of tobramycin other

than 60 mg/ml, nor could it make any representations about the use of TOBI in any nebulizer other than the Pari LC Plus. As with the '269 patent, TOBI is prior art for our purposes.

TOBI became the leading treatment on the market for pulmonary infections in CF patients. One drawback was (and is) that it takes the Pari LC Plus over fifteen minutes to nebulize the 5 ml volume of TOBI. This has led to compliance problems, particularly in children uncomfortable sitting through long treatment sessions. Furthermore, the compressor attached to the Pari LC Plus was (and is) bulky and heavy, rendering the device unportable. It was (and remains) hard for children to immobolize themselves for the required TOBI duration.

In the late 1990's, several companies (other than Chiron) began developing higher efficiency nebulizers. These nebulizers were known as ultrasonic nebulizers, which used vibration of a piezoelectric crystal to create aerosolization. Two such nebulizers are of particular note in this litigation.

First, Aerogen, Inc. came out with the high-efficiency nebulizer known as the AeroDose. The AeroDose is a breath-actuated nebulizer meaning that the nebulizer only produces the atomized liquid during the patient's inhalation phase. (The AeroDose has never been cleared by the FDA.)

Second, at about the same time, Pari Respirator Equipment, Inc. introduced to the market its own high-efficiency nebulizer known as the eFlow. (Pari, it will be recalled, also makes the older model used with TOBI; Pari is not an affiliate of Chiron.) Defendant SourceCF, Inc. serves as the exclusive distributor of the eFlow device, the device at the heart of this controversy.[2] In 2004, the FDA ultimately cleared the eFlow as a device for inhalation of medication (with no limitation as to the particular medication). In contrast to the AeroDose, the eFlow produces a steady stream of aerosolized medication; it is not breath actuated. The eFlow inhaler weighs about as much as an orange and has the diameter of a saucer. The eFlow can operate by battery power. It is more user friendly than the TOBI device and it is more efficient.

[2] Defendant SourceCF Clinical Research & Development, L.L.C. is merely a holding company that has no employees. This order's use of "SourceCF" thus refers to SourceCF, Inc.

On August 14, 2000, plaintiff Chiron acquired PathoGenesis. Chiron thus acquired the rights to TOBI, which it continues to market today. TOBI can be sold, under FDA regulations, only with the older Pari LC Plus nebulizer.

To take advantage of the new generation of nebulizers, defendants herein began promoting the use of the eFlow as a more convenient and more user-friendly way to administer tobramycin solutions to CF victims. The defendants include, as stated, the SourceCF entities, which distribute the eFlow. There are also three pharmacy defendants that dispense concentrations of tobramycin for use in the eFlow: Maxor National Pharmacy Services Corporation (IV Solutions), Foundation Care L.L.C., and Pharmaceutical Specialities, Inc. These latter defendants are licensed pharmacies specializing in what is known as "compounding." Compounding is the manipulation of a medication from its commercial form pursuant to a physician's orders. Such compounding is regulated by the various state boards of pharmacy rather than the FDA. Preparing a tobramycin solution at a specified concentration constitutes compounding. Putting aside patent issues, it is lawful for a physician to prescribe an antibiotic like tobramycin for inhalation with a nebulizer like the eFlow and for pharmacists to fill these prescriptions with vials of the prescribed solutions and sale or rental of the prescribed nebulizer. There is no legal or medical requirement that only FDA-approved drug-device combinations be used.

As more efficient nebulizers were being invented by others, Chiron sought a patent that covered methods of treatment utilizing the new and more efficient nebulizers. This became the '907 patent. Before diving into its history, it is worthwhile to identify two paramount themes: over the entire history of the '907 patent, no '907 study has ever tested a concentration below 60 mg/ml, *i.e.*, all '907 studies tested concentrations at 60 mg/ml (with one exception even more concentrated at 120 mg/ml), *and* no final or interim claim in the '907 patent ever covered any concentrations below "about 60 mg/ml," *i.e.*, all claims called out "about 60 mg/ml" or higher. As will be seen, the '907 disclosure taught away from using weaker concentrations.

On May 18, 2001, a provisional application was filed, docketed as Application No. 60/292,234 (TX 96 at 388). All of the claims in the provisional application indicated

antibiotic concentrations in the range of about 60 mg/ml to about 200 mg/ml. The disclosure was a set of two studies, one involving CF patients and one involving healthy adult patients, comparing the efficiency and efficacy of 60 mg/ml concentrations of tobramycin in the high-efficiency AeroDose, with the commercial concentration of TOBI nebulized in the Pari LC Plus. These two studies were ultimately included in the specification of the final patent. The provisional application's specification also provided (*id*. at 400):

> Formulations according to the invention typically contain from about 60 to about 200 mg, more preferably from about 80 to about 180, and most preferably from about 90 to about 120 mg of aminoglycoside per ml of solution.

On May 12, 2002, a non-provisional application was filed by Chiron with the PTO, docketed as Application No. 10/151,701 (TX 96 at 206). Again, all of the claims were thus limited to concentrations of 60 mg/ml or greater. The specification also contained the two studies from the provisional application plus a third similar study testing different compressors for the Pari LC Plus with a different concentration of tobramycin (at 120 mg/ml). This latter study was also ultimately part of the final '907 disclosure. All of the studies, in other words, involved concentrations at 60 mg/ml or 120 mg/ml.

On October 22, 2002, the patent examiner indicated that Chiron had improperly attempted to merge a patent application for a method of administration with a patent describing a formulation of an antibiotic for inhalation delivery (TX 96 at 359). Apparently during an *ex parte* interview with Chiron's counsel, Chiron indicated a preference to seek a patent of the formulation, thus the remainder of the claims were to be cancelled (*id*. at 361–62). The claims describing the formulation, however, were rejected by the examiner as obvious under 35 U.S.C. 103 in light of the '269 patent (*id*. at 363). On April 22, 2003, Chiron amended its claims (TX 96 at 341). On July 2, 2003, the patent examiner again rejected the claims (TX 96 at 325). The examiner determined that even the amended claims were obvious in light of the '269 patent (*id*. at 329–31).

On December 22, 2003, plaintiff filed a continuation of the earlier application, docketed as Application No. 10/743,529 (TX 96 at 4), which finally survived the critique of anticipation. Once more, none of the claims identified concentrations weaker than 60 mg/ml.

While Chiron's patent application was pending, SourceCF filed an abbreviated new drug application ("ANDA") for approval of a "generic" competitor to TOBI named TOFIN. TOFIN involved a concentration of tobramycin of 100 mg/ml for administration in the high-efficiency nebulizer, the eFlow. TOFIN involved a lower total volume than TOBI and was capable of faster nebulization than TOBI.

On April 20, 2004, Chiron submitted two letters to the FDA regarding SourceCF's ANDA to the FDA (TX 215, TX 216). Among Chiron's criticisms, Chiron contended that TOFIN needed to be tested more, that TOFIN was potentially unsafe, that SourceCF was improperly filing an ANDA when it need to file a new application for approval of a drug-device combination product, that TOFIN was less effective than TOBI, and that SourceCF had misappropriated and misused certain of Chiron's studies (which were ultimately part of the '907 patent). Most notably, according to Chiron, "[t]he petition requests a change in product concentration, volume, total drug content and formulation, and also proposes administration of the new drug product via a delivery system that is unapproved or uncleared as well as different from the delivery system in the approved labeling of the reference listed drug [TOBI]" (TX 216). Chiron also commented "the Petition should be denied because the proposed changes in drug concentration, volume and formulation clearly raise serious questions of safety and effectiveness." Moreover, "small changes in formulation parameters such as osmolality, pH, and inactive ingredients are likely to produce changes in the delivery pattern and therefore have the potential to impact the safety and efficacy of inhaled drug products." The ANDA was ultimately put on hold.

In June 2004, Chiron submitted an amendment to the pending patent application. In this amendment, Chiron sought to add a claim that would have provided a total-dose limitation. Proposed claim 27 would have introduced the limitation of "[a] method of claim 1 wherein at least 20 mg of trobramycin is administered to the patient" (*id.* at 154). On August 11, 2004, an examiner's amendment issued that cancelled claim 27. Chiron thus withdrew that claim.

On May 10, 2005, the '907 patent issued. The primary claim of the '907 patent indicated (col. 63, lines 23–31) (emphasis added):

> 1. A method of treatment of a patient having an endo-bronchial infection comprising administering to the patient for inhalation a nebulized unit dose of 4.0 ml or less of an aqueous solution comprising from *about 60 to about 200 mg/ml* of tobramycin in a physiologically acceptable carrier for a duration of nebulization less than about 10 minutes, using an inhalation device having a rate of aerosol output of not less than about 4μl/sec, that releases at least about 75% of the loaded dose, and that produces aerosol particles having particle sizes between about 1 μm to about 5μm.

No claim in the '907 patent identified a limitation to a particular "total dose" or "respirable dose" of tobramycin. All claims called out concentrations of "about 60 mg/ml"or higher.

* * *

Litigation between these parties began even before the '907 patent issued. An earlier complaint, filed on October 5, 2004, accused defendants of unfair competition under California Business and Professions Code § 17200 (Compl. ¶ 2). After one ruling, *that* lawsuit was dismissed via settlement (*id.* ¶¶ 3–4).

In *this* action, commenced on the day that the patent issued, May 10, 2005, defendants are alleged to infringe, induce infringement of and/or contributorily infringe one or more claims of the '907 patent by (1) selling a product called the eFlow inhaler and (2) instructing doctors and CF victims how to use it. As noted, the defendants in this action are the SourceCF entities, Maxor National Pharmacy Services Corporation (IV Solutions), Foundation Care L.L.C., and Pharmaceutical Specialities, Inc.

At the time of the issuance of the '907 patent, it was uncontested that the compounding pharmacists were dispensing concentrations of tobramycin of 100 mg/ml (the concentration contained in TOFIN) for use in the eFlow device. The parties entered into settlement negotiations almost immediately after the filing of this lawsuit, with defendants essentially conceding that such a concentration of tobramycin fell within the claims of the '907 patent. Shortly after these negotiations, the pharmacy defendants stopped filling prescriptions for concentrations of 100 mg/ml.

On December 1, 2005, upon the stipulated motion of the parties, this Court granted plaintiff the following permanent injunction (at page 6):

> Defendants are preliminarily and permanently enjoined from making, using, offering for sale, selling, promoting or importing into the United States any tobramycin formulation in an aqueous solution comprising from 60 to 200 mg/ml of tobramycin in a physiologically acceptable carrier in a nebulized unit dose volume of 4.0 ml or less for use in the eFlow® Electronic Inhaler by PARI or a similar inhalation device having a rate of aerosol output of not less than about 4μl/sec, releases at least about 75% of the loaded dose, and produces aerosol particles having particle sizes between about 1 μm to about 5μm, for a duration of nebulization of less than about 10 minutes. Defendants are further enjoined from instructing doctors or patients in such use.

By this point, however, the pharmacy defendants had shifted to dispensing concentrations of 40 mg/ml and 50 mg/ml tobramycin for use in the eFlow device pursuant to physicians' orders. Some physicians, however, preferred the higher TOBI concentration and reverted back to TOBI, prescriptions that the pharmacist defendants honored.

Chiron then contended that even concentrations of 50 mg/ml or less violated the patent. An issue remaining after the injunction order, therefore, was whether concentrations of 50 mg/ml or less infringed the '907 patent. Given the narrow scope of the dispute, the Court agreed to advance the trial date. To make this workable for the Court's calendar, no issue of patent invalidity was to be included in the trial. Defense counsel so agreed. An amended case management order set a trial date of April 17, 2006. Defendants then moved for leave to file an amended answer to add for the first time the affirmative defenses of non-infringement, prosecution-history estoppel, patent invalidity for indefiniteness and patent misuse and to assert a counterclaim for declaratory judgment with respect to non-infringement and patent invalidity. When this move threatened to undo the early trial date, the motion was withdrawn by defendants' counsel. Plaintiff dropped its claims for money damages. A bench trial thus commenced on April 17, 2006, limited to the infringement issue. After two sets of closing arguments, this order now follows.

CONCLUSIONS OF LAW

Applying the above factual findings to the law, this order holds that the accused 40 and 50 mg/ml concentrations at issue do not infringe the '907 patent.

1. LITERAL INFRINGEMENT—"ABOUT" AND "APPROXIMATELY" SHOULD BE APPLIED WITH CAUTION.

Chiron did not invent tobramycin. It did not invent any nebulizer, much less the class of newer nebulizers. TOBI was, of course, already known by the time of the '907 application. NEBCIN was likewise already known. Rather, as Chiron explains it, the '907 patent disclosed a concentration range and volume that would be safe and effective with the new generation of nebulizers so as to provide treatment times of less than ten minutes. To have simply used the existing TOBI vials in the newer equipment, Chiron says, would have led to overdoses, given the ability of the newer equipment to atomize the liquid in a more absorbable mist.

The formulation claimed in the '907 patent entailed a "unit dose of 4.0 ml or less of an aqueous solution comprising from about 60 to about 200 mg/ml of tobramycin in physiologically acceptable carrier." A primary question at issue in this litigation is whether concentrations of tobramycin of 50 mg/ml and 40 mg/ml infringe the patent. This requires a determination of how far the term "about" stretches. The Court's December 1 permanent injunction construed "about" to mean "approximately."

Regarding the term "about," the Federal Circuit has noted:

> Such broadening usages as "about" must be given reasonable scope; they must be viewed by the decisionmaker as they would be understood by persons experienced in the field of the invention. Although it is rarely feasible to attach a precise limit to "about," the usage can usually be understood in light of the technology embodied in the invention. When the claims are applied to an accused device, it is a question of technologic fact whether the accused device meets a reasonable meaning of "about" in the particular circumstances.

Modine Mfg. Co. v. U.S. Int'l Trade Com'n, 75 F.3d 1545, 1554 (Fed. Cir. 1996), *cert. denied*, 518 U.S. 1005 (1996) (internal citation omitted); *see also Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995) ("The meaning of the word 'about' is dependent on the facts of a case, the nature of the invention, and the knowledge imparted by the totality of the earlier disclosure to those skilled in the art"). In other words, setting the parameters of "about" in a patent is a difficult and fact-specific task. With the benefit of the trial evidence, this order undertakes this task now.

Viewing the '907 specification and the trial evidence, the terms "about" and "approximately" must be read with caution. However far a concentration might deviate and still be "about" or "approximately" 60 mg/ml, this order finds that the term does not extend to concentrations as low as 50 mg/ml.

First, we must remember that the '907 disclosure consisted solely of three clinical studies. The '907 clinical studies *all* involved concentrations of 60 mg/ml or higher. None involved lower concentrations. The specification — despite its length — never addressed concentrations of tobramycin of less than 60 mg/ml. On the contrary, the specification repeatedly referred to the concentration involved as 60 mg/ml or above. For instance (col. 5, line 62–col. 6, line 3) (emphasis added):

> The aerosol formulations administered in the practice of the invention may comprise from *about 60 to about 200 mg/ml* of aminoglycoside antibiotic. In other aspects of the invention, the aerosol formulations administered in the practice of the invention may comprise from *about 80 to about 180 mg/ml* of aminoglycoside antibiotic. In yet other aspects of the invention, the aerosol formulations administered in the practice of the invention may comprise from *about 90 to about 150 mg/ml* of aminglycoside antibiotic.

Note well that in the above quotation the specified concentrations start at 60 mg/ml and then go higher in concentration, not lower. The specification favored *even higher* concentrations as the preferred embodiment (col. 7, lines 30–34) (emphasis added):

> Formulations according to the invention typically contain from about 60 to about 200 mg, *more preferably from about 80 to about 180*, and *most preferably from about 90 to about 120 mg* of aminoglycoside per ml of solution.

Again, the patent indicated (col. 7, lines 45–48):

> Typically, about 90 to about 120 mg of aminoglycoside antibiotic is dissolved in 1 ml solution of a diluted, typically quarter normal saline containing about 0.225% NaCl.[3]

[3] There are numerous other examples where the '907 patent emphasized and showed preference for specific concentrations: col. 6, line 25; col. 7, line 51 ("high concentrations"); col. 8, lines 21, 37, 42; col. 15, lines 55–58; col. 23, line 14 ("TOBI 90 mg treatment"); col. 26, line 45 ("TOBI 90 mg dose using the Aeroose inhaler were not as high as results achieved by the TOBI 300 mg"); col. 35, line 36 ("at least one of the three TOBI doses (TOBI 90 mg) delivered by the experimental Aerodose inhaler achieved similar actual sputum tobramycin concentrations"); col. 36, line 13 ("present serum tobramycin results demonstrated that TOBI 90 mg delivered by the Aerodose inhaler were similar").

All of the ’907 studies in the specification tested concentrations of 60 mg/ml or higher (120 mg/ml), as will now be summarized.

The first example compared Chiron’s TOBI to a new nebulizer called AeroDose (made by an independent company). That *in vivo* study involved individuals suffering from CF (col. 8, line 55). The study used only 60 mg/ml concentrations of tobramycin: 30 mg in 0.5 ml solution, 60 mg in 1.0 ml solution, and 90 mg in 1.5 ml solution. Those amounts were used with the new AeroDose nebulizer in some patients. This concentration of 60 mg/ml corresponded exactly to the TOBI concentration of 60 mg/ml. Other patients used Chiron’s TOBI combination. The study analyzed the results on several parameters, including nebulization time, efficiency, amount of tobramycin absorbed, and adverse side effects. The study concluded that the AeroDose nebulized the three solution amounts faster and more efficiently than the Pari LC Plus nebulized its total amount of solution.

The second example in the ’907 patent was a “Scintagraphy Study” (col. 37, line 15). Once again, it considered only a concentration of 60 mg/ml. The study compared doses of 60 mg of tobramycin in 1 ml solution inhaled in the AeroDose versus doses of 300 mg of tobramycin in 5 ml of solution. Again, the conclusion was that the AeroDose was more efficient. The second example did *not* suggest that concentrations of less than 60 mg/ml of tobramycin could or should be used.

The last example tested two concentrations: 60 mg/ml and 120 mg/ml. This *in vivo* study compared the Pari LC Plus equipped with a DeVilbiss PulmoAide compressor versus the Pari LC Plus equipped with a Mobiliare compressor (col. 50, lines 48–56). The doses administered to patients with CF were 420 mg of tobramycin in 3.5 ml of solution in the Mobiliare unit and 300 mg of tobramycin in 5 ml of solution in the PulmoAide unit. The study determined that the Mobiliare was faster, more efficient and equally effective as compared to the PulmoAide. As with the first two examples, the third example tested no concentrations of tobramycin below 60 mg/ml.

If it is true, as Chiron asserts, that the ’907 clinical studies were needed to show that concentrations in the indicated range could be effectively and safely used with a more efficient

nebulizer for treatment times less than ten minutes, then the same physical and physiological complexities necessitating the studies in the first place would require one of ordinary skill in the art to use caution in attempting to extrapolate the conclusions in those studies to weaker concentrations. Put differently, small changes in the parameters, Chiron maintains, can lead to dangerous or ineffective results. Under Chiron's own rationale for the invention, it would be imprudent to view the '907 tests as teaching broad conclusions about the interchangeability of the various concentrations and volumes outside the specified range.[4]

Second, the specification of the '907 patent expressly incorporated by reference the '269 patent which, in turn, stated that concentrations below 60 mg/ml were normally ineffective. Recall that the '269 patent was obtained to cover TOBI and was owned by Chiron by the time of the '907 application. The '907 patent expressly incorporated the '269 in full (col. 3, lines 18–33) (emphasis added):

> A preservative-free, stable and convenient formulation of tobramycin (TOBI® tobramycin solution for inhalation; 60 mg/mL tobramycin in 5 mL of 1/4 normal saline) for administration via jet nebulizer was developed by PathoGenesis Corporation, Seattle, Wash. (now Chiron Corporation, Emeryville, Calif.). The combination of a 5 mL BID TOBI dose (300 mg tobamycin) and the PARI LC PLUS/PalmoAide compressor delivery system was approved under NDA 50-753, December 1997, for the management of *P. aeruginosa* in CF patients, and remains the industry standard for this purpose. The aerosol administration of a 5ml dose of a formulation containing 300 mg of tobramycin in quarter normal saline for the suppression of *P. aeruginosa* in the endobronchial space of a patient *is disclosed in U.S. Pat. No. 5,508,269, the disclosure of which is incorporated herein in its entirety by this reference*.

In turn, the '269 specification included the following language about preferred concentrations of tobramycin in the treatment of CF (col. 6, lines 38–47) (emphasis added):

> Typically, two to four, preferably 300 mg of tobramycin is dissolved in 5 ml solution of a diluted quarter normal saline, preferably containing 0.225% NaCl.

[4] In light of Chiron's argument, one must wonder about the upper end of the claimed concentration range. A concentration of 200 mg/ml in a volume of four milliliters is within the claim. This would result in 800 milligrams of tobramycin, a large amount, being inhaled by children in a brief period; compare this to the 300 milligrams inhaled using TOBI and less efficient absorption equipment over more time. None of the '907 studies vetted such methods.

> The most preferred aerosol tobramycin formulation according to the invention contains 300 mg of tobramycin sulfate per 5 ml of the quarter normal saline. *This corresponds to 60 mg/ml of tobramycin which is minimal yet efficacious amount of tobramycin to suppress the Pseudomonas aeruginosa infection in endobronchial space*.

The '269 patent provided (col. 8, lines 3–41) (emphasis added):

> The formulated dose of 60 mg/ml of one quarter diluted saline has been found to be optimal for the most efficacious delivery. Although in some instances both lower or higher doses, typically from 40–80 mg/ml may be advantageously used, the 60 mg/ml dose of tobramycin is preferred. A more concentrated tobramycin solution has three disadvantages. First, if the solution approaches the solubility of tobramycin, 160 mg/ml, precipitation on storage is expected. Second, a higher concentration of tobramycin than is clinically needed is economically disadvantageous. Thirdly, a more concentrated solution will increase the osmorality of the solution, thus decreasing the output of the formulation with both jet and ultrasonic nebulizers. The alternative of a more concentrated solution in a smaller total volume is also disadvantageous. Most nebulizers have a dead space volume of 1 ml, i.e., that of the last 1 ml of solution is wasted because the nebulizer is not performing. Therefore, while for example, a 2 ml solution would have 50% wastage, the 5 ml solution (the capacity of the nebulizer) has only 20% wastage. Additionally, since there is no sufficient aerosolization of the drug into the small particles, the drug in large particles or as a solution is deposited in the upper airways and induces cough and may also cause bronchospasm. Large aerosol particles also limit the drug delivery.
>
> *The dose lower than 60 mg of tobramycin of diluted saline is not sufficient to suppress the bacterium and to treat the infection. Lower concentrations of tobramycin will not be sufficiently effective in at least 90% of patients.* This is due to variability of sputum tobramycin levels caused by anatomical variability among patients as observed in Examples 4 and 5, and also because the minimum inhibitory concentration of *Pseudomonas aeruginosa* also varies. As seen in Table 4, a dose of 300 mg total has been found to be optimal. Previously studied doses 80 mg, *Pedia Pulmonol*., 6:91–8 (1989) were reported effective, however, the dose would be predicted to be efficacious in approximately sixty to seventy percent of patients initially. If any degree of drug resistance developed, only a small percentage of patients would be effectively treated.

One issue raised by this language is an estoppel to invoke the doctrine of equivalents to reach concentrations weaker than 60 mg/ml. That issue will be considered below. For the immediate purpose of literal infringement, the quoted language further supports a cautious reading of the term "about."

In brief, although the earlier patent noted that "in some instances both lower or higher doses, typically from 40–80 mg/ml may be advantageously used" ('269 patent, col. 8, lines 3–4), the remainder of the language was an unequivocal critique of concentrations below 60 mg/ml. The '269 patent described the 60mg/ml concentration as the concentration "which is minimal yet efficacious," "optimal," and "preferred." Lower concentrations were deemed "not sufficient to suppress the bacterium and to treat the infection" and "will not be sufficiently effective in at least 90% of patients." In light of this critique, the limits of about 60 to about 200 mg/ml set forth in the '907 patent must be read narrowly.

Third, the trial evidence was persuasive that the phrase "about 60 mg/ml" would ordinarily be understood by those practicing such methods to refer to the limits of the pharmacy's professional measuring capabilities. Pharmacists typically provide actual concentrations within two to five percent of the prescribed concentrations. Put differently, doctors prescribe with precision, *e.g.*, "60 mg/ml. They do not prescribe "about 60 mg/ml." The pharmacists then dispense at concentrations, subject only to the industry-acceptable limits of their equipment and professional capabilities, which, as stated, the trial evidence established are two to five percent. Pharmacists cannot substitute a different concentration. The word "about" refers to the range of tolerances prevailing in the subject field.

In short, the specification of the '907 patent, the three examples in the '907 patent, the incorporated '269 patent, and the measuring capabilities of the profession all lend a narrow and cautious meaning to the word "about." This rules 50 mg/ml as outside the literal scope of the patent.

2. DOCTRINE OF EQUIVALENTS.

Chiron next asserts infringement under the doctrine of equivalents. "The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 732 (2002). "[A] patentee may invoke this doctrine to proceed against the producer of a device 'if it performs substantially the same function in substantially the same way to obtain the same result.'" *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950) (internal

citations omitted). "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 370 F.3d 1131, 1139 (Fed. Cir. 2004) (*citing Festo*, 535 U.S. at 733).

"The doctrine of equivalents must be applied on an element by element basis." *Phillips Petroleum Co. v. Huntsman Polymers Corp.*, 157 F.3d 866, 877 (Fed. Cir. 1998) (*citing Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997)). Moreover, under the "all limitations" rule, "an accused product or process is not infringing unless it contains each limitation of the claim, either literally or by an equivalent." *Freedman Seating Co. v. Am. Seating Co.* 420 F.3d 1350, 1358 (Fed. Cir. 2005).

A. ESTOPPEL.

Under certain circumstances a patent owner is barred from relying on the doctrine of equivalents. *See, e.g., Honeywell,* 370 F.3d 1131, 1140–41. "A particular structure can be deemed outside the reach of the doctrine of equivalents because that structure is clearly excluded from the claims whether the exclusion is express or implied." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1345 (Fed. Cir. 2001); *see also Gaus v. Conair Corp.*, 363 F.3d 1284, 1291 (Fed. Cir. 2004) ("[T]he patentee cannot reclaim that surrendered claim coverage by invoking the doctrine of equivalents"); *Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co., Inc.*, 384 F.3d 1333, 1342 (Fed. Cir. 2004) ("The specification's clear disavowal of nonsurfactant solubilizers precludes the application of the doctrine of equivalents to recapture the disavowed solubilizers"). The test for such "specification disclaimer estoppel" thus is whether the patentee *clearly disclaimed* the contested scope.

Application of such estoppel is a legal question, not a question of fact. "A patent applicant may limit the scope of any equivalents of the invention by statements in the specification that disclaim coverage of subject matter. Such limitations on the scope of equivalents are legal determinations." *Frank's Casing Crew & Rental Tools, Inc. v.*

Weatherford Int'l, Inc., 389 F.3d 1370, 1376 (Fed. Cir. 2004) (*citing J & M Corp. v. Harley-Davidson, Inc.*, 269 F.3d 1360, 1366 (Fed. Cir. 2001)).

As noted above, the '907 patent expressly incorporated the '269 patent by reference "in its entirety." "To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000); *see also Manual of Patent Examining Procedure*, § 2163.07(b) (8th ed. 2006). This order holds that the '269 specification must be deemed in its entirety to be part and parcel of the '907 specification.[5]

As stated, the '907 patent plainly and explicitly incorporated the entirety of the '269 patent. We must now consider whether this disclaimed concentrations of less than 60 mg/ml.

To reiterate the key portions cited above, the '269 patent stated that (col. 6, lines 42–47):

> The most preferred aerosol tobramycin formulation according to the invention contains 300 mg of tobramycin sulfate per 5 ml of the quarter normal saline. This corresponds to 60 mg/ml of tobramycin which is minimal yet efficacious amount of tobramycin to suppress the *Pseudomonas aeruginosa* infection in endobronchial space.

Again, the '269 patent stated (col. 8, lines 3–7, 28–31):

> The formulated dose of 60 mg/ml of one quarter diluted saline has been found to be optimal for the most efficacious delivery. Although in some instances both lower or higher doses,

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[5] "Whether and to what extent material has been incorporated by reference into a host document is a question of law." *Advanced Display*, 212 F.3d at 1283. Any incorporated material must be considered in interpreting the host document. "When a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein." *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001). Indeed, the whole point of incorporation by reference is to make the material part of the patent:

> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. *The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.*

Manual of Patent Examining Procedure, § 2163.07(b) (8th ed. 2006) (emphasis added).

It does not matter that the '269 patent is a different patent with different inventors. A patentee may, in fact, incorporate by reference any source "which is available to the public." *In re Howarth*, 654 F.2d 103, 106 (C.C.P.A. 1981).

> typically from 40–80 mg/ml may be advantageously used, the 60 mg/ml dose of tobramycin is preferred.
>
> * * *
>
> The dose lower than 60 mg of tobramycin of diluted saline is not sufficient to suppress the bacterium and to treat the infection. Lower concentrations of tobramycin will not be sufficiently effective in at least 90% of patients.

The overt critique of concentrations less than 60 mg/ml places our case within the four corners of Federal Circuit precedent limiting the reach of the doctrine of equivalents. In *SciMed*, *supra*, the Federal Circuit explained:

> As noted above, the common specification of SciMed's patents referred to prior art catheters, identified them as using the dual lumen configuration, and criticized them as suffering from the disadvantages of having "larger than necessary shaft sizes" and being "stiffer in their distal regions than would be desired." That criticism of the dual lumen configuration was consistent with the evidence from SciMed witnesses and documents, which noted the advantages of the coaxial lumen configuration in increasing the flexibility of catheters and their ability to track through the coronary arterial system. The disclaimer of dual lumens was made even more explicit in the portion of the written description in which the patentee identified coaxial lumens as the configuration used in "all embodiments of the present invention."

SciMed, 242 F.3d at 1345 (internal citations omitted). In *SciMed*, just as in the instant case, the patentee did not state that the dual lumen configuration was completely useless, but did describe in detail the disadvantages of that alternative configuration. Accordingly, the opinion ruled that "[h]aving specifically identified, criticized, and disclaimed the dual lumen configuration, the patentee cannot now invoke the doctrine of equivalents to 'embrace a structure that was specifically excluded from the claims.'" *Ibid*. (*quoting Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 400 (Fed. Cir.1994)).[6]

Likewise, a similar result was reached in *Dawn Equip. Co. v. Kentucky Farms Inc.*, 140 F.3d 1009, 1016 (Fed. Cir. 1998). The Federal Circuit there overturned a jury verdict finding infringement under the doctrine of equivalents. The opinion explained that:

[6] It is also worth noting that the disclaimer need not be in response to an action by the United States Patent Office. *See Festo*, 535 U.S. at 736. While defendants have not pointed to any aspect of the prosecution history of the '269 patent suggesting office action, neither was such a fact suggested in *SciMed*.

> The patent teaches that such mechanisms are time-consuming to adjust and are prone to misadjustment by inserting the pin in the wrong holes, and furthermore the loose pins in such mechanisms are easily lost. Kentucky Farms' multiple-hole, pinned height-adjustment mechanism is such a mechanism and shares these same problems.

Ibid. (internal citations omitted). Accordingly, "[t]hese statements in the patent alone strongly suggest, if not mandate, judgment in Kentucky Farms' favor."

Plaintiff relies on *Micro Chemical v. Great Plains Chemical Company*, 194 F.3d 1250, 1260 (Fed. Cir. 1999), for its argument that simply critiquing prior art in a later patent is not sufficient to clearly disavow those claims in the later patent. In *Micro Chemical*, the Federal Circuit ruled that inclusion of a prior art reference that contained certain limitations could not be translated as a disclaimer for purposes of the later patent. The decision stated:

> In restricting the scope of the apparatus and method claims to cover only a cumulative weigh system, the district court read the patentee's statements about the Brewster prior art as a clear disavowal of the weigh dump method. To the contrary, although the applicant noted certain inefficiencies in the Brewster system, the patent never clearly disavows the weigh dump method as being incapable of performing the claimed functions. The statements relied on by the district court in both the background section and the prosecution history were directed to a particular prior art device, the Brewster machine, not to the weigh dump method in general.
>
> The background section notes that the Brewster machine "weighed and then dispensed each additive separately and sequentially." The background section further explains that this machine "was unsuccessful because it was too slow and too inaccurate for handling additive concentrates in a feedlot environment." Nothing, however, directly attributes the failures of the Brewster machine to anything other than its particular design. The patentee did not at any time assert that the weigh dump method itself is the reason for the inaccuracies or slowness of the Brewster system.

Ibid.

But the inventors' critique of the prior art patent here is different from the critique in *Micro Chemical*. It is true that there is a difference in the two patents — the '269 patent involved a low-efficiency nebulizer, not the high-efficiency nebulizer used in the '907 patent. The '907 inventors, however, did not rely on the earlier patent just to criticize the slow nebulization time involved. Rather, they explicitly relied on the earlier patent as guiding the

way for the proper concentration of tobramycin to put in the new high-efficiency nebulizer. Indeed, it is unpersuasive for Chiron to contend that the '269 patent's teachings on concentration were criticized in the later '907 patent when the later patent contained very similar language about the efficacy of tobramycin concentrations below 60 mg/ml. As stated, the '907 patent, just like the '269 patent, provided (col. 7, lines 30–34):

> Formulations according to the invention typically contain from about 60 to about 200 mg, more preferably from about 80 to about 180, and most preferably from about 90 to about 120 mg of aminoglycoside per ml of solution.

Given that the '907 patent not only incorporated the earlier patent but perpetuated its expression of the preferred tobramycin concentrations, this order finds that plaintiff is estopped from proving infringement by equivalence.

B. 50 MG/ML NOT EQUIVALENT TO ABOUT 60 TO 200 MG/ML.

Even if plaintiff were not estopped from relying on the doctrine of equivalents, defendants' formulations of tobramycin of 50 mg/ml and 40 mg/ml would not infringe the '907 patent via the doctrine of equivalents.

An expansive view of equivalency is inappropriate where, as here, the patent involves, at most, a modest improvement over the prior art. As the Federal Circuit has explained:

> . . . while a pioneer invention is entitled to a broad range application of the doctrine of equivalents, an invention representing only a modest advance over the prior art is given a more restricted (narrower range) application of the doctrine. When a patentee claims an improvement over an earlier invention, other parties are entitled to practice variations of that prior invention, so long as they are not the same as, or an equivalent of, the improvement claimed by the patentee.

Thomas & Betts Corp. v. Litton Systems, Inc., 720 F.2d 1572, 1580 (Fed. Cir. 1983); *see also GMI Holdings, Inc. v. Stanley Door Sys., Inc.*, 943 F. Supp. 1420, 1427 (N.D. Ohio 1996) ("a pioneer invention, one which represents a major advance over the prior art, is entitled to a broad and liberal application of the doctrine of equivalents, while one that adds little to the state of the art is not"). The Supreme Court has also expressed general skepticism about broad readings of the doctrine of equivalents. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997) ("There can be no denying that the doctrine of equivalents, when applied broadly,

conflicts with the definitional and public-notice functions of the statutory claiming requirement").

Here, as indicated above, the '907 patent represented at most a modest improvement. Chiron did not invent tobramycin. Chiron did not invent high-efficiency nebulizers. Chiron did not invent even low-efficiency nebulizers. Chiron did not invent inhalation therapy. As stated, the '907 patent disclosed nothing about concentrations lower than 60 mg/ml and called out concentrations higher than 60 mg/ml (90 mg/ml to be precise) as the preferred embodiment. Via the '269 incorporation, the patent itself taught away from weaker concentrations as effective.

Chiron asserts that its '907 studies established the medically-appropriate concentration and volumes suitable for use with the new generation of nebulizers. In its most favorable light to Chiron, the '907 studies proved that the standard 60 mg/ml TOBI dose of 5 ml could be reduced to 1.5, 1.0 and 0.5 ml and still remain effective when used with the new generation of nebulizers. Chiron has emphasized the inherent complexities and tradeoffs with small variations portending large possible variations as justifying the patent in the first place. If so, the teaching of the '907 studies must be viewed with caution, as stated above. Accordingly, a wide swath of equivalents would be unreasonable. Chiron has not proven that one of ordinary skill in the art would regard the accused methods as an insubstantial change from the methods taught or claimed in the patent in suit or would regard the accused methods to use substantially the same concentrations as the disclosed or claimed methods.

Contrary to Chiron, a "hypothetical claim analysis" does not supersede all other requirements of the doctrine of equivalents. A "hypothetical claim analysis" is used to test the validity of supposed equivalents *against the prior art*. It asks whether a hypothetical claim covering the range of asserted equivalents "could have been allowed by the PTO over the prior art." *Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 684 (Fed. Cir. 1990). If the answer is yes, then Chiron asserts the doctrine of equivalents inquiry is over — equivalence has been shown. This is wrong.

Before any "hypothetical claim analysis" comes into play, the doctrine of equivalents must otherwise be satisfied and the equivalence issue must have devolved to whether the prior art would have anticipated or rendered obvious the proposed scope of equivalents, thus preventing application of the doctrine of equivalents. In analyzing the latter, it may be useful to pose the question of whether a hypothetical claim — drawn to cover the asserted equivalents — could have been allowed by the PTO over the prior art.

Here, however, the immediate problem is not the prior art. It is the fact that the '907 tests taught little (if anything) about concentrations below 60 mg/ml. That is not a prior art problem. It is a specification/disclosure problem. The problem is also that the '907 disclosure expressly taught away from concentrations below 60 mg/ml. That also is not a prior art problem. It is a specification/disclosure problem. Put differently, one of ordinary skill in the art would *not* view the accused method as an insubstantial change from the teaching of the patent. The fundamentals of the doctrine have not been met in the first place. Chiron is wrong in asserting, therefore, that *Abbott Laboratories v. Dey, L.P.*, 287 F.3d 1097, 1105–07 (Fed. Cir. 2002), somehow collapsed the entire doctrine of equivalents into a "hypothetical claim analysis."

The thrust of Chiron's case is that total dose — not concentration — is the essential consideration. This would read the concentration limitation out of the claim. According to Chiron, the total dose used in the accused methods falls within the total dose reachable via concentrations covered by the claim. For example, if 100 mg in 1 ml is within the claim, Chiron argues that 100 mg in 2 ml should also be deemed within the claim since the total dose is still 100 mg.

The doctrine of equivalents cannot be used to vitiate an entire claim limitation. As the Federal Circuit instructed:

> . . . courts must consider the totality of the circumstances of each case and determine whether the alleged equivalent can be fairly characterized as an insubstantial change from the claimed subject matter without rendering the pertinent limitation meaningless.

Freedman, 420 F.3d at 1359. When Chiron filed this action, it argued vociferously that defendants were infringing the patent by dispensing *concentrations* of 100 mg/ml. When

defendants ceased using any concentration within the range, Chiron reversed field and advanced its current argument that the concentration limitation should, in effect, be ignored.

Under Chiron's view, concentration would become meaningless. This became glaringly obvious during the testimony of Chiron's expert witnesses. For example, plaintiff presented testimony from Dr. Warren Finlay, an expert in aerosol science and aerosol delivery systems of medications (Tr. 165–66). According to this expert's math, the potential concentration and the accused concentration result in similar amounts of tobramycin being captured in the lungs (Tr. 189). But his methodology wound up proving too much. When he was asked to run the numbers for even weaker concentrations, *i.e.*, concentrations at 30 mg/ml or less, the difference in lung-captured amounts was yet again small. His methodology tended to prove that almost any weak concentration would still infringe.

Similarly, Dr. Gerald Smaldone, plaintiff's expert in aerosol science and aerosol delivery systems of medication, used a methodology that proved too much. He testified (Tr. 119):

> Q: In your opinion, Doctor, does it — does a change in concentration from 60 to 50 to 40 in the context of the '907 patent, and in comparing that to the defendants' formulations, is that kind of change meaningful in any way with regard to what these formulations are designed to do?
>
> A. In my opinion, there's no difference between any of these formulations that are described in the patent, because what they're all designed to do is to provide the same nebulizer dose, and I've tried to illustrate in my calculations that they're all covered by the claims in that patent.

Later, he testified "I mean, there's no way to distinguish the formulations at 50 milligrams per ml from the 60 milligrams per ml solution. They provide the same nebulized dose" (Tr. 123). So, too, concentrations of 40 and 60 mg/ml are "completely interchangeable," according to Dr. Smaldone (Tr. 124). The Court then asked Dr. Smaldone to consider concentrations of 30 mg/ml in a 3.4 ml total dose (Tr. 144). In response, Dr. Smaldone testified that the example given by the Court would infringe under his methodology and, indeed, resulted

in a total dose (about 100) greater than a lower total dose (80) he had already testified was an infringing equivalent.[7]

Chiron also points to the PTO examiner's reasons for allowance as further support that the '907 patent was not concerned with concentration. The examiner noted that the novel features of the '907 invention, as compared to the '269 patent, "reside in requiring 10 minutes or less for duration of nebulization, with an inhalation device having a rate of aerosol output of not less than 4µl/sec that releases at least 75% of the loaded dose and that produces particle sizes of between about 1µ to about 5µ" (TX 96 at 141). More than suggesting that the concentration limitation contained in the '907 was trivial, it appears the examiner simply did not think the concentration described was different from the '269 patent. After all, the '907 patent, the '269 patent and TOBI all described concentrations of at least 60 mg/ml and the '907 patent incorporated the '269 patent's teachings (and disavowals) regarding concentration. The concentration in the '907 did not expand the boundaries of tobramycin concentrations for inhalation (such as by demonstrating that weaker concentrations could be used). Instead, the method of this patent reiterated that the concentration was to be kept at 60 mg/ml or higher. The patent must be limited by that reasoning.[8]

Chiron extolled the importance of concentration in its letters to the FDA in response to SourceCF's ANDA for TOFIN in 2004 (TX 215, TX 216). As noted above, Chiron informed the FDA that the change in concentration from TOBI to TOFIN (60 mg/ml to 100 mg/ml) could have significant consequences on the safety and efficacy of the medication. It is true, as Chiron argues, "that the quantum of proof necessary for FDA approval is significantly higher than that

[7] Given that Chiron places such emphasis on the *Abbott* opinion, *supra*, it is worth noting that Chiron's expert testimony provides another distinction from *Abbott*. In *Abbott*, the Federal Circuit found that the district court erred in its hypothetical claim analysis by concluding that Abbott's experts would have completely eviscerated all boundaries to the claimed range at issue. The Federal Circuit concluded that Abbott would not be precluded from relying on the doctrine of equivalents because the application "does not eliminate the upper limit of phospholipid from the claim." 287 F.3d at 1107. Here, as Chiron's experts made clear, on their view, there would be no lower boundary. It was evident from the expert that there would be almost no concentration too weak to fall outside of Chiron's proposed range of equivalents.

[8] This is further substantiated by the fact that Chiron *withdrew* proposed claim 27, which would have described a claim in terms of total dose, not concentration (TX 96 at 154). The Federal Circuit has deemed that such an amendment can limit a patent holder's ability to reclaim the withdrawn limitation via the doctrine of equivalents. *See, e.g.*, *Honeywell*, 370 F.3d at 1141.

required by the PTO." *Purdue Pharma L.P. v. Endo Pharmaceuticals Inc.*, 438 F.3d 1123, 1134 (Fed. Cir. 2006). This order, therefore, does not view Chiron's letters as conclusive admissions of non-equivalence. Chiron's representations to the FDA at the least, however, indicate that Chiron has long agreed that small changes in concentration *are* non-trivial.

Finally, Chiron also argues "[d]efendants' own witnesses testified, and their own documents reflect, that their 50 mg/ml and 40 mg/ml formulations are *deliberately designed* to deliver an equivalent respirable dose as compared to the enjoined 100 mg/ml formulations" (Br. 4) (emphasis in original). There is some truth to this charge but it does not carry the day, for the following reasons.

Before the patent issued, defendants promoted their eFlow therapy as delivering an "equivalent respirable dose" to TOBI (TX 6). "Respirable dose" means the amount of tobramycin absorbed into the lungs (Tr. 120). Due to its efficiency, the eFlow nebulizer could, it was claimed, deliver as much absorption as TOBI while using less solution than TOBI and taking less time. Before the patent issued, the eFlow promotion was based, as Chiron points out, on a concentration of 100 mg/ml.

After the patent issued, defendants eventually began promoting the two weaker concentrations at issue. This was done to respect Chiron's patent rights (TX 30). The promotion, however, still portrayed the eFlow therapy as delivering a respirable dose "equivalent" to that delivered by TOBI. This time, of course, the promotion featured weaker concentrations than those called out by the '907 patent (TX 72A).

With some exceptions, defendants are correct that the equivalence was drawn to TOBI and that TOBI is prior art for our purposes.[9] But this is not a satisfactory answer, for the point was to achieve TOBI's effectiveness but in less time with the newer equipment, like the inventors.

[9] The exceptions occurred after the patent issued. Instead of drawing a parallel to TOBI, they drew a parallel to the pre-patent eFlow therapy using 100 mg/ml (TX 30; TX 45; TX 72A; Sledge Depo. 208). For the reasons stated in the text, however, the decisive factor is that the result was not achieved in the same way as the patented method.

The convincing point of distinction lies elsewhere. Although defendants have used the word "equivalent," nowhere have they stated that the method promoted was equivalent to the method patented. Rather, they have said that the respirable dose delivered by each method is equivalent. At most, this admitted that the *result* achieved is the same.[10] But the key is that the result is not achieved in the same *way*. The basics of inhalation therapy and even TOBI were already known. The supposed invention was the discovery that concentrations at about 60 mg/ml or higher could be safely and effectively administered via the more efficient nebulizers. That *lower* concentrations could also be safely and effectively used was discovered by *defendants*. For the reasons stated earlier, the '907 patent did *not* teach use of the lower concentration. It taught away from using lower concentrations as ineffective. Based on what was the supposed discovery of the '907 patent, one of ordinary skill in the art would not have understood that the weaker concentrations at issue would have been safe and effective or merely an insubstantial change from the patented method. The use of the specified concentration range was an integral step in the patented method. The accused methods may well achieve the same *result* but it gets there via a different *way*.

3. ISSUES NOT REACHED.

This order does not address the potential invalidity of the '907 patent. The patent in suit is in the category of "medical-method patents." The validity of such patents is controversial. *See* Donald S. Chisum, *Chisum on Patents*, § 1.03[2][d][3] (2005). The Federal Circuit, however, has approved the validity of some medical-method patents and this Court need not determine the issue here. As noted, the Court agreed to advance the trial date. The parties in turn agreed to narrow scope of the dispute to make this schedule workable, including agreeing not to argue patent invalidity at trial.

This order also does not address whether the claims in the '907 patent constitute "step-plus-function" or "means-plus-function" limitations under 35 U.S.C. 112 ¶ 6. Of course, if Paragraph 6 were to apply, "a claim term will cover nothing more than the corresponding

[10] It must be noted that the '907 contains no claim limitation for a certain "respirable dose." Indeed, nowhere in the specification does "respirable dose" appear. So too for the '269 patent. The only use of the word respirable at all in the '907 specification is in relation to "respirable" *particles* (col. 49, lines 37–40).

structure or step disclosed in the specification, as well as equivalents thereto." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1367 (Fed. Cir. 2002). A recent legal issue that has arisen is the interplay between Paragraph 6 limitations and method patents. *See* Chisum, § 18.03[5][e][iii]. This order, however, finds that defendants did not infringe the patent in suit on other grounds and thus need not reach this issue.

CONCLUSION

For the foregoing reasons, this order finds that the 40 mg/ml and 50 mg/ml concentrations in dispute do not infringe the '907 patent under any theory. Judgment for defendants will be entered accordingly.

IT IS SO ORDERED.

Dated: May 16, 2006.

WILLIAM ALSUP
UNITED STATES DISTRICT JUDGE